National PBM Drug Monograph

Iloprost Inhalation Solution (Ventavis®)

March 2005

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

FDA Approved Indications: Iloprost is a synthetic prostacyclin analogue that inhibits adenylate cyclase thus increasing intracellular cyclic AMP levels leading to vasodilation of the systemic and pulmonary arterials. Iloprost is approved for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III/IV symptoms.

Dosing: Inhalation of iloprost should be achieved using the Prodose® AAD® nebulizer system. Initially a dose of 2.5mcg should be given. If the dose is tolerated, subsequent doses should be increased to 5mcg. Iloprost should be given 6-9 times per day (no more than every 2 hours) while awake based on the patients need and tolerability. The maximum daily dose evaluated in studies was 45mcg (5mcg 9 times per day).

Safety: The most common adverse events associated with iloprost include cough, flushing, headache, and jaw pain. Cough, flushing, and headache were all reported as transient and resolved within a limited amount of time. Syncope is the only serious adverse event reported but did not reach statistical significance. This could potentially be because pulmonary hypertension can cause syncope.

Iloprost has not been studied specifically in the geriatric population, caution should be used as there is often a greater frequency of hepatic, renal, and cardiac dysfunction as well as concomitant drug therapy.

Efficacy: Iloprost has been approved in Europe for the treatment of primary pulmonary hypertension since September 2003, and in Australia since January 2004. There has been one randomized controlled trial and numerous open label trials evaluating the safety and efficacy of iloprost in pulmonary hypertension. The studies all confirmed that iloprost was effective in increasing the distance walked in a 6 minute walk test as well as improving NYHA functional class and improving hemodynamic profiles. As mentioned above, the adverse events were minor and usually transient. Long term safety and efficacy data has not been evaluated thoroughly, but appears to show sustained effects without increases in adverse events.

Conclusion: Pulmonary arterial hypertension is a disease with limited treatment options. Intravenous prostacyclin had previously been shown to be the most efficacious for treatment but came with numerous problems due to the need for continuous infusions. Iloprost is a drug that offers the same, if not better, effectiveness as IV prostacyclin without all the complications.

Recommendation:

It is recommended that iloprost inhalation solution be available for nonformulary use based on patients meeting criteria for use.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating Iloprost Inhalation Solution for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1-2]

Iloprost is a synthetic prostacyclin analogue that inhibits adenylate cyclase thus increasing intracellular cyclic AMP levels leading to vasodilation of the systemic and pulmonary arterials. It has also been shown to have some effect on platelet aggregation but the extent of this is unknown. Iloprost is primarily metabolized by beta-oxidation of the carboxyl side chain but in vitro studies showed minor metabolism by the cytochrome P450 system. The absolute bioavailability of inhaled iloprost has not been determined but is estimated in some articles about 80%. Approximately 60% of iloprost is protein bound primarily to albumin.

Iloprost has a half-life of 20-30 minutes. Following inhalation, iloprost was not detectable in the plasma 30-60 minutes later. Peak serum concentrations of iloprost are approximately 150 pg/ml. Due to the short half-life, frequent administration is required.

FDA Approved Indication(s) and Off-label Uses[1]

Iloprost is approved for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III/IV symptoms. This drug was approved on December 29, 2004.

Current VA National Formulary Alternatives

Currently there are no therapeutic treatment options for pulmonary hypertension on the VA National Formulary.

Dosage and Administration[1-2]

Inhalation of iloprost should be achieved only with the Prodose® AAD® nebulizer system. Initially a dose of 2.5mcg should be given. If the dose is tolerated, subsequent doses should be increased to 5mcg. Iloprost should be given 6-9 times per day (no more than every 2 hours) while awake based on the patients need and tolerability. The maximum daily dose evaluated in studies was 45mcg (5mcg 9 times per day).

Iloprost should not be mixed with any other medications before nebulization. Each nebulizer treatment takes about 5 minutes for the 2.5mcg dose and 10 minutes for the 5mcg dose. Iloprost is packaged in single-use ampuls that contain 20mcg/2ml. One ampul is required for each dose to deliver 5mcg to the mouthpiece. Any remaining solution should be discarded after each treatment.

Caution should be used in patients with hepatic dysfunction as iloprost elimination is impaired in this population. Patients not on dialysis do not require dose adjustments of iloprost. However, caution should be used in patients receiving dialysis as the effect of this is not known.

Efficacy

Efficacy Measures

Change in hemodynamics is an important outcome in all of the trials. The pivotal randomized trial looked at change from baseline in pulmonary artery pressure (normal: 9-18mmHg), pulmonary vascular resistance (normal: 20-130 dyn·sec/cm^5), systemic arterial pressure (normal: 70-105mmHg), right atrial pressure (normal: 2-8 mmHg), pulmonary artery wedge pressure (normal: 2-10mmHg), heart rate (normal: 60-100bpm), cardiac output (normal: 2.5-4.2 L/min/m^2), arterial oxygen saturation, mixed venous oxygen saturation.

The 6 minute walk test is an effective way of measuring clinical efficacy in patients with pulmonary arterial hypertension. This test is usually performed at baseline and then following treatment. The 6 minute walk test is a predetermined course that the patient walks on to determine how far they can walk. The goal is to be able to walk significantly farther following treatment.

Improvement in NYHA functional class was also considered an important measure. In the pivotal trial, a combined endpoint of an increase of ≥ 10% in distance walked in 6 minutes and an improvement in NYHA functional class during 12 weeks was considered the primary outcome.

Summary of efficacy findings[3-10]

Iloprost has been approved in Europe for the treatment of primary pulmonary hypertension since September 2003, and in Australia since January 2004. There has been one randomized controlled trial and numerous open label trials evaluating the safety and efficacy of iloprost in pulmonary hypertension. The studies all confirmed that iloprost was effective in increasing the distance walked in a 6 minute walk test as well as improving NYHA functional class and improving hemodynamic profiles. As mentioned above, the adverse events were minor and usually transient. Long term safety and efficacy data has not been evaluated thoroughly, but appears to show sustained effects without increases in adverse events.

The results of a randomized controlled trial found that iloprost had better outcomes compared with placebo. Almost 25% of the patients in the iloprost group had improvements in the NYHA functional class compared with only 13% of the placebo group (p=0.03). A greater than 10% increase in distance walked in 6 minutes was seen in 37.6% of iloprost group and 25.5% of placebo group (p=0.06). A combined endpoint showed 16.8% improvement in the iloprost group compared with 4.9% in the placebo group (p=0.007). Results were similar to open label trials conducted.

One study reported by CoTherix® followed 63 patients for 12 weeks and found that there was a significant improvement in NYHA functional class. Walking distance and Mahler Dyspnea Index also appeared to be higher in the iloprost group compared with conventional therapy. Patients were followed for 2 additional years but results are unknown.

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 9).

Adverse Events (Safety Data)[1, 3-10]

Deaths and Other Serious Adverse Events

There have been few reported deaths with iloprost in the trials of this agent. The pivotal trial reported 1 death in the iloprost group versus 4 deaths in the placebo group during the 12 week study (p=0.37). A limited number of deaths were reported in the open label studies but it is uncertain whether these were caused by iloprost or worsening of disease. Iloprost was shown to have a higher incidence of syncope than placebo in the pivotal study but was not reported in any other trial.

Common Adverse Events
The most frequently reported adverse events were flushing, cough, and jaw pain. Flushing and cough were transient and resolved after a short amount of time. Results from pivotal trial are seen below. Other trials showed cough, headache, flushing and jaw pain at similar rates or not at all.

	Iloprost (n=101)	Placebo (n=102)	p-value
Cough	39	26	0.05
Headache	30	20	0.11
Flushing	27	9	0.001
Flu Symptoms	14	10	0.39
Peripheral Edema	13	16	0.69
Nausea	13	8	0.26
Jaw Pain	12	3	0.02
Hypotension	11	6	0.22
Diarrhea	9	11	0.81
Vertigo	7	11	0.46

The package insert also lists the following adverse events reported by at least 4 iloprost patients and reported at least 3% more than placebo patients:

	Iloprost	Placebo
Trismus	12	3
Insomnia	8	2
Vomiting	7	2
Alkaline Phosphate Increased	6	1
Back Pain	7	3
Abnormal Lab Test	7	3
Tongue Pain	4	0
Palpitations	7	4
Syncope	8	5
GGT Increased	6	3
Muscle Cramps	6	3
Hemoptysis	5	2
Pneumonia	4	1

Tolerability
Iloprost was well tolerated in the studies. Adverse events was not a reason for discontinuation of iloprost in any of the trials. Unlike the IV formulation, tolerance does not appear to be a problem with

inhaled iloprost. Dose escalation with IV formulation could lead to increased side effects with the need for closer monitoring.

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 9).

Precautions/Contraindications

Precautions

Iloprost solution should not come into contact with skin, eyes or be orally ingested. This medication should not be mixed with other medications prior to administration. Iloprost has not been evaluated in patients with COPD, severe asthma, or acute pulmonary infections.

While initiating iloprost therapy, vital signs should be monitored due to the risk of syncope. Iloprost should not be initiated if a patient's systolic blood pressure is less than 85 mmHg. Caution should be used with concomitant drugs or conditions that increase the risk of syncope. Of note, syncope is a symptom of pulmonary arterial hypertension especially with physical exertion. Exertional syncope may suggest a medicinal gap or insufficient efficacy, and dose adjustment or a change in therapy may be necessary.

Although not specifically studied, caution should be used in geriatric patients as there is often a greater frequency of hepatic, renal, and cardiac dysfunction as well as concomitant drug therapy.

Treatment should be stopped immediately if signs/symptoms of pulmonary edema occur as this may be a sign of pulmonary venous hypertension.

Iloprost contains a pregnancy category C rating. There are no adequate studies in pregnant women and therefore, iloprost should only be used if the benefit outweighs the potential risks to the fetus. It is unknown if iloprost is excreted in human milk. Because many drugs are excreted in human milk and there is potential for serious side effects in the infant, nursing should be discontinued.

Contraindications

There are no known contraindications.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name iloprost:

	Potential Severity	Probability
Bimatoprost ophthalmic	Minor	Uncommon
Lantanoprost ophthalmic	Minor	Uncommon
Travoprost ophthalmic	Minor	Uncommon

LA/SA for trade name Ventavis®:

	Potential Severity	Probability
Ventolin Inhalation	Moderate	Occasional
Ventuss Syrup	Minor	Uncommon
Tavist Syrup	Minor	Uncommon

Drug Interactions[1]

Drug-Drug Interactions

Iloprost has the potential to increase the hypotensive effects of vasodilators and antihypertensive agents. There is also a potential for increased risk of bleeding due to platelet inhibition especially in patients maintained on anticoagulants. In vitro studies suggest that there is no relevant inhibition of cytochrome P450 drug metabolism.

Data Compilation Tables[3]

Increase of ≥ 10% in distance walked in 6 minutes and an improvement in NYHA functional class during 12 weeks

Outcome on Drug	16.8%
Outcome on Placebo	4.9%
Relative Risk Reduction (95%CI)	243%
Absolute Risk Reduction (95% CI)	11.9%
NNT (95%CI)	8

Acquisition Costs

Iloprost was approved by the FDA in December 2004. It is expected to be marketed by late first quarter of 2005 however, no definite date has been set by the manufacturer. Iloprost inhalation will be distributed by a specialty network of pharmacies which can be reached at a central call center which has yet to be established (877-483-6828). The Prodose® AAD® system will also be available from the same pharmacies and can be ordered at the same time. Information about Prodose® AAD® has been requested from the company. Acquisition costs will be updated as they become available.

Pharmacoeconomic Analysis

There are no formal pharmacoeconomic analyses available for iloprost.

Conclusions[11]

Pulmonary arterial hypertension is a disease with limited treatment options. Chest guidelines have been established using evidence-based criteria as published in 2004. These guidelines have created an algorithm for treating patients with pulmonary arterial hypertension with functional class II-IV.

These guidelines state that all patients should receive general care when indicated including oral anticoagulants, diuretics, oxygen, and digoxin. Patients should then undergo acute vasoreactivity testing which would determine their treatment course. Oral calcium channel blockers are first-line therapy for patients with positive vasoreactivity and should continue until the response diminishes. Functional class III patients that failed vasoreactivity testing could use oral bosentan, IV epoprostenol, subcutaneous treprostinil, oral berprost, or inhaled iloprost as first line therapy. Chronic IV treatment with epoprostenol, bosentan, treprostinil or iloprost is reserved as first line therapy in functional class IV patients.

Oral bosentan is often considered first line therapy for patients with pulmonary hypertension because of cost and ease of use. Although there are currently no studies comparing iloprost with bosentan, there are two randomized controlled studies evaluating change in distance walked in 6 minutes in patients taking bosentan. The first study, randomized 32 patients to receive bosentan 125mg BID or matching placebo for a minimum of 12 weeks (max=28 weeks).[12] This study found that patients in the bosentan group had an increase in distance walked in 6 minutes of 70 meters while placebo patients had no change from baseline ($p<0.0001$). This study also showed that there was a significant improvement in functional class in the bosentan group ($p=0.039$). A second trial randomized 213 patients to bosentan 125mg BID, bosentan 250mg BID or matching placebo for a minimum of 16 weeks (max=28 weeks).[13] The results showed an increase of 35 meters in the bosentan 125mg BID patients, 54 meters in the bosentan 250mg BID patients, and a decrease of 8 meters in placebo patients. The combined bosentan groups had a 36 meter increase ($p<0.001$). Like the previous study there was similar improvement in functional class noted. Both studies found that there were few adverse events noted. The trial that examined patients on 250mg of bosentan did report elevated LFT's in a few patients which resolved when the drug was removed. This finding was found to be dose dependent and it is felt that at 125mg, bosentan is safe to use.

Patients with WHO functional class IV pulmonary hypertension were excluded from the bosentan trials which is important to note as it is unknown if similar results would be seen in these patients. The iloprost trials, included patients with class IV pulmonary hypertension and did show significant improvement . Although the results from the iloprost trials as well as the bosentan trials all used the 6 minute walk test as primary endpoints, it is difficult to compare the results. The bosentan trials looked at overall change from baseline while the iloprost studies reported results in terms of percent improvements from baseline. Both drugs do appear to slow the progression of disease as well as improve quality of life for patients.

All of the treatment options come with advantages and disadvantages. Berprost and bosentan are oral products allowing for easy administration but berprost appears to lose it's effectiveness with time while bosentan has been associated with abnormal hepatic function and anemia. Subcutaneous treprostinil showed significant improvement in trials but came with pain, erythema and induration at the site in almost all patients. Intravenous prostacyclin had previously been shown to be the most efficacious for treatment but came with numerous problems due to the need for continuous infusions such as infection, continuous monitoring, tolerance, possible systemic side effects. Iloprost is a drug that offers the same, if not better, effectiveness as IV prostacyclin without as many of the aforementioned complications. It was shown in clinical trials to improve NYHA functional class, increase the distance walked in 6 minutes and improve hemodynamic profile. Short term data shows minor side effects that are usually transient. Long term safety data has not been looked at extensively but preliminary results appear to show sustained effects without significant adverse events.

Recommendations

It is recommended that iloprost inhalation solution be available for nonformulary use based on patients meeting criteria for use.

References:

1. Ventavis (Iloprost) Inhalation Solution. South San Francisco, CA: CoTherix, Inc., 2004.
2. Goldsmith DR, Wagstaff AJ. Inhaled Iloprost: In Primary Pulmonary Hypertension. Drugs 2004; 64 (7): 763-773.
3. Olschewski H, Simonneau G, Nazzareno G, Higenbottam T, Naeije R, et al. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002; 347: 322-329.
4. Hoeper MM, Schwarze M, Ehlerding S, Adler-Schuermeyer A, Spiekerkoetter E, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. N Engl J Med 2000; 342: 1866-1870.
5. Olschewski H, Ghofrani HA, Schmehl T, Winkler J, Wilkens H, et al. Inhaled iloprost to treat severe pulmonary hypertension: An uncontrolled trial. Ann Intern Med 2000; 132: 435-443.
6. Wensel R, Opitz CF, Ewert R, Bruch L, Kleber FX. Effects of iloprost inhalation on exercise capacity and ventilatory efficiency in patients with primary pulmonary hypertension. Circulation 2000; 101: 2388-2392.
7. Olchewski H, Walmrath D, Schermuly R, Ghofrani HA, Frimminger F, et al. Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. Ann Intern Med 1996; 124: 820-824.
8. Hoeper MM, Olschewski H, Ghofrani HA, Wilkens H, Winkler J, et al. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. J Am Coll Cardiol 2000; 35: 176-182.
9. Ventavis Medical Information. South San Francisco, CA: CoTherix, Inc., 2005.
10. Badesch DB, McLaughlin VV, Delcroix M, Vizza CD, Olschewski H, et al. Prostanoid therapy for pulmonary arterial hypertension. J Am Coll Cardiol 2004; 43: 56S-61S.
11. Badesch DB, Abman SH, Ahearn GS, Barst RJ, McCrory DC, et al. Diagnosis and the management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004; 126 (1).
12. Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomized placebo-controlled study. Lancet 2001; 358: 1119-23.
13. Rubin LJ, Badesch DB, Barst RJ, Nazzareno Galie, Black CM, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002; 346: 896-903.

Prepared March 2005. Prepared by: Danielle Alsip, PharmD.

Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to August 2004) using the search terms iloprost and Ventavis®. The search was limited to studies performed in humans and published in English language. Reference lists of review articles were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

<table>
<tr><th>Citation
Design
Analysis type
Setting</th><th>Eligibility Criteria</th><th>Interventions/
Patient Population Profile</th><th>Efficacy Results</th><th>Safety Results</th><th>Author's conclusions</th></tr>
<tr>
<td>Olschewski (2002)[3]

MC PC RCT
European Specialist Centers</td>
<td>Inclusion criteria: PPH, Non-PPH, mPAP >30 mmHg, 6 min walk test=50-500meters, NYHA class III or IV.

Major Exclusion criteria: prostanoids, beta-blockers, CCB ≥ 6 weeks, PWP >15mmHg at rest, CI <15 at rest or >4L/min/m^2 BSA, bleeding disorder, FVC <50%, FEV in 1 sec < mean normal value</td>
<td>Drug--Iloprost
Route--Inhalation
Dose—2.5-5 mcg, 6-9 times daily (mean 7.5 x/day) (91% on 5mcg)
Duration—12 weeks

<table>
<tr><th></th><th>Iloprost</th><th>placebo</th></tr>
<tr><td>Age</td><td>51.2</td><td>52.8</td></tr>
<tr><td>Male</td><td>31.7%</td><td>33.3%</td></tr>
<tr><td>PPH</td><td>50.5%</td><td>50%</td></tr>
<tr><td>NYHA III</td><td>59.4%</td><td>57.8%</td></tr>
<tr><td>6 min walk</td><td>332 m</td><td>315 m</td></tr>
</table>
</td>
<td>N$_R$ = 203 (101 iloprost)

Primary Outcomes
<table>
<tr><th>NYHA Class Improvement</th><th>Iloprost</th><th>Placebo</th></tr>
<tr><td>2 classes</td><td>1%*</td><td>0%</td></tr>
<tr><td>1 class</td><td>23.8%*</td><td>12.7%</td></tr>
<tr><td>6 Minute walk test**</td><td>37.6%§</td><td>25.5%</td></tr>
<tr><td>Combined end point</td><td>16.8%^</td><td>4.9%</td></tr>
</table>
*p=0.03 compared with placebo
**≥ 10% increase
§p=0.06 compared with placebo
^p=0.007 compared with placebo

Secondary Outcomes:
-Change in distance walked in 6 minute walk test was significantly higher in iloprost group (p=0.04)
-Significantly more improvement in NYHA class in iloprost (p=0.03)
-Significant improvement in quality of life (p=0.026)</td>
<td>
<table>
<tr><th></th><th>Iloprost</th><th>placebo</th><th>p</th></tr>
<tr><td>Syncope</td><td>5</td><td>0</td><td>0.03</td></tr>
<tr><td>Cough</td><td>39</td><td>26</td><td>0.05</td></tr>
<tr><td>Flushing</td><td>27</td><td>9</td><td>0.001</td></tr>
<tr><td>Jaw Pain</td><td>12</td><td>3</td><td>0.02</td></tr>
</table>
More patients in placebo group did not complete the study due to death, discontinuation of study medication, withdrawal of consent, but mostly due to deterioration, insufficient clinical benefit or both.
</td>
<td>-Iloprost improves combined end point of NYHA class and 6 minute walk test.
-Iloprost improved many secondary outcomes.
-Benefit was similar to epoprostenol and bosentan which are current therapies.
-Efficacy and safety of inhaled iloprost was demonstrated
-With advantages over continuous IV infusion, iloprost is a suitable alternative to</td>
</tr>
<tr>
<td>Hoeper (2000)[4]
Open Label</td>
<td>Inclusion criteria: PPH, NYHA III or IV
Exclusion criteria: secondary PH, severe right heart failure on catecholamines, patients lost to follow-up.</td>
<td>Drug—Iloprost
Route—Inhalation
Dose—Initial 100mcg/day ÷ 6-8 doses; maintenance 150mcg/day in 6 patients after 3 months
Duration—12 months

Co-medications when indicated: anticoagulants, diuretics, digoxin and CCB if already taking

Demographics:
Avg. Age—38 (22-65)
Sex—15 females, 9 males
NYHA—20 class III, 4 class IV</td>
<td>N$_R$ = 31; 24 followed up with study MD
<table>
<tr><th></th><th>Baseline</th><th>3mo</th><th>12mo</th></tr>
<tr><td>mSAP</td><td>98</td><td>93*</td><td>90*</td></tr>
<tr><td>mPAP</td><td>59</td><td>52*</td><td>52*</td></tr>
<tr><td>mRAP</td><td>8</td><td>5*</td><td>5*</td></tr>
<tr><td>CO</td><td>3.8</td><td>4.0*</td><td>4.4*</td></tr>
<tr><td>PVR</td><td>1205</td><td>1001*</td><td>925*</td></tr>
<tr><td>SVR</td><td>2088</td><td>1884*</td><td>925*^</td></tr>
<tr><td>SV</td><td>46</td><td>50*</td><td>55*^</td></tr>
<tr><td>Vo_2</td><td>62</td><td>65*</td><td>67*</td></tr>
<tr><td>6MWD</td><td>278</td><td>353*</td><td>363*</td></tr>
</table>
*p<0.05 compared with preinhalation variables at 3mo or 12 mo with baseline
^p<0.05 compared with preinhalation variables at 12 mo with 3 mo</td>
<td>-Cough was common during first days of treatment but resolved within first 4 weeks.
-5 patients reported flushing, headache, jaw pain but were mild.
-No reports of syncope reported</td>
<td>-Beneficial effects on exercise capacity and hemodynamic variables in PPH
-No patients discontinued due to side effects
-5 out of 24 had no clinical response to iloprost
-Appears to be safe and effective for PPH</td>
</tr>
</table>

Citation Design Analysis type Setting	Eligibility Criteria	Interventions/ Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions
Olschewski (2000)[5] Open Label Uncontrolled	Inclusion Criteria: clinical instability defined as the occurrence of at least 1 of the following: -decrease in 6 min walk test by ≥30% in 1-2 months -CVP ≥17 mmHg during rest -cardiogenic edema refractory to diuretics -hepatic/renal failure	Drug—iloprost Route—inhalation Dose—8.4-10.5 mcg 6-12x/day Co-medications: diuretics, anticoagulation, CCB Demographics: Age—39 years old NYHA—4 class III, 15 class IV	N=19 Primary Outcomes: Confined to Bed: Baseline 9, 3 months 4 6 min walk test: Baseline 8 (189m), 3 months 9 (362m) Died: Baseline --, 3 months 4 *p=0.048 Secondary Outcomes: -mPAP and PVR decreased from baseline (p<0.01) at 3 months -PAP, PVR, CVP, CI improved at 3 months (p<0.05) -1 patient switched to IV prostacyclin -4 patients had lung transplants -7 still receiving therapy at study end	Cough confirmed in 2/7 patients reporting	-Improvement of right ventricular function w/substantial improvement in exercise capacity and hemodynamics. -Rescue strategy for patients with PH and right heart decompensation that is refractory to conventional therapy.
Wensel (2000)[6] Open Label	Inclusion Criteria: NYHA class III, mPAP > 30 mmHg and exclusion of secondary causes	Drug—iloprost Route—inhalation Dose—17mcg 6x/day Co-medications: CCB (5), oral anticoagulants (9), diuretics (11), O_2 (3) Demographics—41 years old	N=11 (10 PPH, 1 NPPH) Primary Outcomes: mPAP: Baseline 65.2, After Dose 59.5 mRAP: 7.7, 6.5 CO: 4.1, 5.2 SVR: 1760.1, 1445 PVR: 1508.5, 1175.3 Exercise Duration: 379 sec, 438 sec *p>0.05	No ADR reported	-Affects pulmonary hemodynamics, symptoms and possibly survival. -Compared w/IV provides non-invasive administration while avoiding side effects. -No ADR reported. -Disadvantage of having drug fluctuations throughout the day.
Olschewski (1996)[7] Open Label Uncontrolled	Inclusion Criteria: PPH, NYHA class III/IV	O_2—2-8L/min Inhaled NO—10-28 ppm IV prostacyclin—at highest tolerated dose x 20 min Inhaled prostacyclin—x15 min Inhaled iloprost—9-21 mcg Tests were spaced so patient would return to baseline in between. Trials were done twice in 1 month and averaged.	N=6 (4 PPH and 2 w/PPH due to CREST) Inhaled NO PAP: Baseline 60.4, After 54.2* CO: 2.8, 3.48* PVR: 1578, 1141** MAP: 13.7, 10.2** SVR: 2413, 2064* VO_2 Sat: 57, 62.7* IV Prostacyclin	No ADR reported	-Iloprost dose is less than IV -Iloprost results were same as inhaled prostacyclin but effects lasted longer.

Citation Design Analysis type Setting	Eligibility Criteria	Interventions/ Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions
			<table><tr><th></th><th>Baseline</th><th>After</th></tr><tr><td>CO</td><td>2.94</td><td>4.52**</td></tr><tr><td>PVR</td><td>1551</td><td>1000**</td></tr><tr><td>MAP</td><td>100</td><td>87**</td></tr><tr><td>SVR</td><td>2453</td><td>1398**</td></tr><tr><td>HR</td><td>101.8</td><td>106.5**</td></tr><tr><td>VO_2 Sat</td><td>53.4</td><td>66.7**</td></tr></table> Inhaled iloprost/prostacyclin <table><tr><th></th><th>Baseline</th><th>After</th></tr><tr><td>PAP</td><td>62.3</td><td>50.8**</td></tr><tr><td>CO</td><td>2.75</td><td>4.11**</td></tr><tr><td>PVR</td><td>1721</td><td>1019**</td></tr><tr><td>CVP</td><td>13.6</td><td>10.2*</td></tr><tr><td>SVR</td><td>2400</td><td>1680**</td></tr><tr><td>AO_2 Sat</td><td>90.6</td><td>93.8*</td></tr><tr><td>VO_2 Sat</td><td>51.1</td><td>66.3**</td></tr></table>*p=0.05, **p=0.01 -Iloprost had same results as inhaled prostacyclin except results lasted for 60-120 min vs. 10-30 min -Iloprost was continued in 1 patient for 1 year and pulmonary response was sustained, NYHA class improved from IV to III.		
Hoeper (2000)[8] Open Label	Inclusion Criteria: diagnostic criteria of NIH for PPH. Exclusion Criteria: significant coagulopathy, severe airway obstruction, coronary/cerebrovascular event w/in 3 months, liver/kidney impairment	Inhaled NO at 40 ppm followed by iloprost at 14-17 mcg during right heart catheterization. Demographics: Age—46 years old NYHA—6 class II, 18 class III, 11 class IV CCB—15 on low dose	N=35 (19 females, 16 males) NO vs. Iloprost <table><tr><th></th><th>NO</th><th>Iloprost</th></tr><tr><td>mSAP</td><td>94</td><td>86</td></tr><tr><td>mPAP</td><td>55</td><td>52</td></tr><tr><td>CO</td><td>3.7</td><td>4.2</td></tr><tr><td>CI</td><td>2.1</td><td>2.4</td></tr><tr><td>SVR</td><td>2024</td><td>1597</td></tr><tr><td>PVR</td><td>1159</td><td>920</td></tr><tr><td>PaO_2</td><td>68</td><td>73</td></tr><tr><td>SvO_2</td><td>60</td><td>66</td></tr></table>P<0.05 for iloprost vs. NO	-No ADR reported with NO -5 patients had headache and flushing after iloprost which resolved after a couple of minutes. -1 patient had jaw pain with iloprost	-Iloprost exhibited a favorable hemodynamic response. -Iloprost was significantly more potent in decreasing mPAP and PVR and increasing CO than NO. -Iloprost was well tolerated with no major side effects.

N_R, Number randomized. PPH—Primary Pulmonary Hypertension. Non-PPH associated w/appetite suppressants, scleroderma, in operable chronic thromboembolus. PWP—pulmonary artery wedge pressure. CI—cardiac index. mSAP—mean systemic arterial pressure (mmHg). mPAP—mean pulmonary arterial pressure(mmHg). mRAP—mean right atrial pressure(mmHg). CO—cardiac output (liters/min). PVR—pulmonary vascular resistance (dyn*sec*cm^{-5}). SVR—systemic vascular resistance(dyn*sec*cm^{-5}). SV—stroke volume (ml/beat). Vo_2—mixed venous oxygen saturation (%). 6MWD—6 minute walk distance (m). PaO_2—arterial oxygen tension. SvO_2—mixed venous oxygen saturation.